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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,471	10/06/2000	Lorenzo Williams	0459-0490P	8775
2292 7596 01/28/2004 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER GAKH, YELENA G	
			ART UNIT 1743	PAPER NUMBER

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/880,471	WILLIAMS, LORENZO	
Examiner	Art Unit	
Yelena G. Galkh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 December 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 463 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 5-30, 32, 34-38 and 40-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-30, 32, 34-38 and 40-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other _____

DETAILED ACTION

1. RCE and Preliminary Amendment, filed on 12/10/03 and Supplemental Amendment filed on 01/14/04, are acknowledged. Claims 1-2, 5-30, 32, 34-38 and 40-43 are pending in the Application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not disclose the method of separating products on TLC plate by electrophoresis without any modification of TLC plate, e.g. by attaching electrodes to it. It is not clear, how such separation can be performed with a plain TLC plate.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. **Claims 1-2, 5-12, 15-30, 33-36 and 42-43** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta et al. (US 6,306,590 B1) in view of Frank (IDS).

Mehta discloses microfluidic matrix localization apparatus and method for "**screening, manipulating and assessing fluidic reagents, reagent mixtures, reaction products (including the products of DNA sequencing reaction) and the like.** The invention provides integrated systems for performing a variety of chemical, biochemical and biological experiments and other fluidic operation, including PCR, DNA sequencing, **integrated or sequential screening of chemical or biological libraries**, and the like" (col. 5, lines 25-34). The invention is based on a surprising discovery "that the PCR reaction can be performed in the presence of a variety of sieving matrices, including: agarose, linear polyacrylamide, methyl-cellulose, polyethylene oxide and hydroxy ethyl cellulose and that resulting PCR products are separated in the microfluidic devices" (col. 4, lines 40-45). "In preferred embodiments, the components of the PCR reaction mixture are mixed with the sieving matrix in a microfluidic channel, e.g., a channel on a LABCHIPTM. The apparatus can include one or more additional channels crossing the microfluidic channel, and optionally includes fluid (or joule heating) means such as an electrokinetic controller. Detection regions in the channels, and corresponding detectors are also useful. The PCR products are typically **electrophoresed** through the channels to achieve product separation. It will be appreciated that separations chips comprising a **single matrix separations phase** are produced as described above, thus, **for this embodiment, multiple fluidic phases in the apparatus are not necessary.** However, additional fluidic phases can be placed in additional channels or channel regions in fluid communication with a channel region comprising the PCR sieving mixture for electrophoretic or electroosmotic movement of the PCR

components or products in the chips. For example, in some aspects a PCR reaction product is selected for further manipulations such as cloning, sequencing or the like, all of which are performed in PCR chips (see also, USSN 60/068,311, entitled "Closed Loop Biochemical Analyzer" by Knapp, filed Dec. 19, 1997 and U.S. Pat. No. 6,235,471" (col. 17, lines 29-52).

Thus, the PCR products are prepared in a bulk of a stationary phase (a mix with the sieving matrix) and separated in the same bulk, with optional addition of detection regions in the channels (screening of the compounds).

Mehta further teaches that the substrates of the microfluidic devices are made of glass, quartz, silicon, polymers, (col. 6, lines 5-10), as well as silica gels (col. 9, lines 45-65) and activated aluminas (col. 10, lines 3-14), and that they may optionally include a planar element which overlays the channeled portion of the substrate, enclosing and fluidly sealing the various channels, wells and other microfluidic elements (col. 6, lines 35-40). The devices "are from about 0.01 to about 0.1 cm thick" (col. 6, lines 52-53). Mehta mentions such analytical (screening) techniques as "autoradiography, spectroscopy, microscopy, photography, mass spectrometry, nuclear magnetic resonance and many other techniques for observing and recording the results of mixing reagent", as well known methods of screening of the reaction products (col. 1, lines 5-15).

Mehta does not specifically disclose screening of the separated products in the same bulk stationary phase by **biological or biochemical methods**.

Frank discloses a method for preparing and screening a plurality of compounds on a matrix support by synthesizing a library of compounds on a stationary phase and screening them by biological or biochemical methods, as described in section "Antibody Binding Assay" (p. 9224).

It would have been obvious for anyone of ordinary skills in the art to apply a specific screening step, involving biological or biochemical methods, disclosed by Frank, in Mehta's method, because Mehta indicates a screening step as a part of her invention involving biologically important compounds, and Frank demonstrates the efficiency and straightforwardness of the method of synthesis and **biological or biochemical** screening of libraries of biologically important compounds directly on the same substrate.

Although Mehta in view of Frank do not specifically disclose a TLC plate, it would have been obvious for anyone of ordinary skills in the art to perform synthesis, separation of the products and their screening on the TLC plate, because TLC plate is conventionally used for separation and screening compounds; Mehta's synthesis is directed toward PCR products, which are conventionally separated by electrophoresis, and which therefore requires applying electrical field and the chip setting, which is not required for many other reactions and which therefore can be obviously conducted on much simpler and cheaper TLC plate.

It would have been obvious for anyone of ordinary skill in the art to use any of the liquid phase mixtures recited in claim 28, because choosing the solvent mixture for developing TLC plate is a routine procedure in analytical chemistry.

7 **Claims 13-14** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta in view of Frank, as applied to claims 1-2, 5-12, 15-30, 33-36 and 42-43 above, and further in view of Hudak (US 6,034,361).

Although Mehta discloses "thermocycling in microscale devices, including thermocycling by joule heating", Mehta in view of Frank do not teach microwave-assisted synthesis.

Hudak emphasizes in the Background of the Invention, that using microwave heating to promote the progress of one or more sample preparation steps or chemical synthesis steps is well known in the art (col.1, lines 14-16).

It would have been obvious for anyone of ordinary skill to use microwave radiation to provide "joule heating" in Mehta-Frank's method, because Mehta teaches necessity of "joule heating" for PCR, and Hudak demonstrates an easy way to provide it with microwave radiation. It would have been obvious to place the bulk of the stationary phase with the reagents into a microwave cave to provide such heating.

8. **Claims 37-38** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta in view of Frank, as applied to claims 1-2, 5-12, 15-30, 33-36 and 42-43 above, and further in view of Bataillard (US 5,482,372) or Brocklehurst et al. (US 5,739,003).

Mehta in view of Frank do not specifically disclose detection of biological effects of a compound interacting with a microorganism or enzyme as a screening step.

Bataillard mentions "enzymatic assays and drug screening using microorganisms" (col. 2, lines 38-40); Brocklehurst emphasizes that "drugs, e.g. antibiotics, must be screened for activity against particular microorganisms and the concentration required for achieving that effect must be determined" (col. 1, lines 32-35).

It would have been obvious to modify Mehta-Frank's method specifically for creating and screening drug libraries by using microorganisms in the screening step, because such step is standard in screening drugs, as disclosed by Bataillard or Brocklehurst.

9. **Claims 40 and 41** are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta in view of Frank, as applied to claims 1-2, 5-12, 15-30, 33-36 and 42-43 above, and further in view of the well-known prior art discussed by Wolfbeis (DE 3,701,833 A1).

Mehta in view of Frank do not particularly disclose detection of catalytic activity produced by observed changes in absorption of light or detection of fluorescence due to a cleaved substrate.

Wolfbeis mentions "known methods for the optical determination of the catalytic enzyme activity of a sample, which use enzyme substrates which are cleaved under the influence of the enzyme to be measured and decompose to colored or fluorescent products, where the increase in color or fluorescence intensity per unit time is regarded as a measure of the enzymatic activity" (Abstract).

It would have been obvious for anyone of ordinary skills in the art to conduct spectroscopic analysis of the substrate in order to determine the enzymatic (catalytic) activity of the compounds, as disclosed in the prior art discussed by Wolfbeis, in modified Mehta-Frank's bulk stationary phase, because this is a conventional way for determining enzymatic activity of the compounds, which can be readily obtained by modified Mehta-Frank's method.

Response to Arguments

10. Applicant's arguments filed 10/14/03 and supplemental arguments filed 01/14/04 have been fully considered but they are not persuasive.

First, the examiner would like to notice that Mehta invention is not directed mainly toward PCR reaction, as can be concluded from the Applicant's arguments. Rather, the PCR

reaction is used as one of the examples of conducting complex reactions, along with separation and screening the products on a single substrate. Two last steps are considered intrinsic features of the method, since one of the main discoveries of the inventors is the fact that such complex biochemical reactions as PCR can be conducted in a separating media. If it were not for separation (and following screening) of the products, then why should it be necessary to conduct PCR reaction in such an unconventional media? The reactions demonstrated by the Applicant as the examples are also quite well known and give known products. Therefore, the examiner does not agree with the applicant's statement that "the identification and separation steps [of Mehta's method] are not as relevant in comparison to identification and separation steps in the present invention where *de novo* product synthesis occurs". The applicant further argues: "furthermore, Mehta teaches the use of gel electrophoresis for the separation technique. Gel electrophoresis is performed on a polyacrylamide bulk phase. On the other hand, in the present invention, the synthesis, separation and screening steps are all performed on a TLC plate". This statement is very confusing in light of the applicant's own disclosure: "in a further embodiment of the invention the bulk of stationary phase comprises a polyacrylamide gel enclosed between two glass or plastic backing plates. For this embodiment, the separation step typically involves electrophoresis" (page 7, lines 10-13, also claims 18, 29 and 30). All following applicant's remarks regarding electrophoresis stand against enablement of his own disclosure regarding electrophoresis. Does this mean that the disclosure related to this embodiment is not enabled, contrary to what is disclosed in the specification? Moreover, Mehta's method is not limited to electrophoresis, with all sort of possible chromatographic separation media listed for using in separation. Mehta is dealing with a more complex case of PCR synthesis, which requires electrophoretic separation; however, it is absolutely obvious that electrophoresis is not the only separation technique that can be used for separating products of reactions, especially if reactions are chemical, rather than biochemical. Again, citing Mehta "using the apparatus and methods [of the present invention], it is possible to perform many or all of the fluidic operations needed for an experiment or diagnostic procedure in an integrated fashion in a single apparatus. The present invention provides apparatus, systems and methods for dramatically increasing the speed and simplicity of screening, manipulating and assessing fluidic reagents, reagent mixtures, reaction products (including the products of DNA sequencing reactions) and the like. The

invention provides integrated systems for performing *a variety of chemical, biochemical and biological experiments and other fluidic operations*, including PCR, DNA sequencing, integrated or sequential screening of chemical or biological libraries, and the like. Although the microfluidic systems of the invention are generally described in terms of the performance of chemical, biochemical or biological reactions separations, incubations and the like, it will be understood that, as fluidic systems having general applicability, these systems can have a wide variety of different uses, e.g., as metering or dispensing systems in both biological and nonbiological applications" (col. 5, lines 20-40).

Further, the applicant refers to Example 2 of Mehta's disclosure, where PCR is performed at higher temperature in methylcellulose media. It should be noted, that both conditions – higher temperatures and methylcellulose media are meant to be used in some embodiments of the instant method; therefore it is not clear, what is the difference between these conditions and those described by Mehta?

Regarding Frank's reference – the only modification of Mehta's method that Frank teaches is specific biochemical and biological screening methods of separated products. Mehta indicates many screening techniques that can be applied in her method, Frank is more specific regarding application of biological and biochemical screening. Any routineer in the art would be motivated to apply specific biological and biochemical screening methods taught by Frank to separated compounds in Mehta's method, which intrinsically comprises separation and screening.

Regarding sequential synthesis: PCR comprises sequential synthesis, and Mehta several times refers specifically to sequential reactions. Moreover, creating chemical or biological libraries, to which Mehta refers in col. 5, lines 33-34, presumes sequential reactions.

Again, the examiner cannot agree that Mehta and Frank separately disclose parts of the invention, since Mehta teaches all features of the invention, except for minor modification, i.e. specific techniques of screening, taught by Frank. The motivation of combining two references is apparent to any routineer in the art.

Supplemental arguments¹ regarding multiple phases: "it will be appreciated that separations chips comprising *a single matrix separation phase* are produced as described above, thus, *for this embodiment, multiple fluidic phases in the apparatus are not necessary*" (col. 17,

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lines 39-42) It is not quite clear, what is meant by moving reagents in two or even three dimensions. Returning to electrophoresis – the applicant proposes using electrophoresis instead of chromatography – exactly what Mehta is teaching. Is it one-dimensional or two-dimensional? The examiner is confused regarding using such terminology. Since the front is moving in one direction, then chromatography is one-dimensional. There exist two- and higher-order dimensional chromatography, but it involves different techniques and presumably is not what the applicant meant in his disclosure. If the applicant proposed using 2D or 3D chromatography, or the method, which involves migrating reagents and products in more than one dimension, then the examiner agrees, that such embodiment is not enabled by Mehta. However, no such embodiment is recited in the claims, and the embodiments that are recited in the claims read on combination of Mehta and Frank, along with other references cited in the Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1700.

Yelena G. Gakh
1/22/04

Yelena Gakh